

Attorney Docket No.:
CARR-0084 (103216.00252)

PATENT

REMARKS

Pending in this Application are Claims 1, 3, 5, 7, 13 – 15, 17, and 23 – 25.

I. Rejections Under 35 U.S.C. §103(a)

Claims 1, 3, 5, 7, 13 – 15, 17, and 23 – 25 stand rejected under 35 U.S.C. §103(a) as being unpatentable over European Patent No. 307847 (“EP 307847”), U.S. Patent No. 4,996,050 (“U.S. ‘050”), or International Patent Application No. WO 82/03772 (“WO 82/03772”), in view of European Patent No. 619370 (“EP 619370”), U.S. Patent No. 5,589,451 (“U.S. ‘451”), U.S. Patent No. 5,814,605 (U.S. ‘605”), International Patent Application No. WO 97/13857 (“WO 97/13857”), or International Patent Application No. WO 98/16243 (“WO 98/16243”). The Examiner has asserted that the claims are unpatentable because the combination of a growth factor protein and a protease enzyme is obvious due to the fact that both components are used **individually** in the art for the same purpose.

The Examiner asserts that the individual components are both used “with treating blood related conditions, such as wound healing.” See Final Office Action, Page 3.

However, although two or more agents may be used for treating the same blood related conditions, they may act on totally different aspects of the condition. For example, **growth factors are used to stimulate cell proliferation in a wound, whereas proteases are used to remove or digest debris in a wound as a so-called wound debrider.** Thus, simply because the components are used in treatment of similar conditions, **it does not follow that the components will be compatible in their modes of operation.**

The Examiner asserts that “Applicant argues that just because the components are used individually in the art for the same purpose that there would have been no way that one of ordinary skill in the art would have had any idea to combine them.” See Final Office Action, Page 4. **This is a mischaracterization of Applicants’ argument.** Applicants respectfully assert that common knowledge in the art teaches away from the combination of a growth factor protein and a protease enzyme and **that it is not obvious to combine two components which are inherently antagonistic.** Applicants respectfully assert that the Examiner has not considered nor addressed whether there was a reasonable expectation of success or motivation in the art to combine the antagonistic components, nor whether the prior art and common knowledge teach away from the combination of a protein and a protease enzyme, nor whether Applicants proceeded contrary to the accepted wisdom in the art to reach the current claims.

Although obviousness does not require absolute predictability, **at least some degree of predictability is required.** Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. See *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). Proteins in actuality show varying degrees of activity, stability, and degradation in a mixture with protease enzymes. See Specification, Page 19, lines 5 – 12. **There would have been no reasonable expectation of successfully producing an effective composition for**

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treatment of injuries by combining a particular growth factor protein with a particular protease enzyme, based on the knowledge that the components are not only antagonistic, but antagonistic in unpredictable and varying degrees. As discussed in the Specification, the protease plasmin or plasminogen does not inactivate the growth factor KGF, but does inactivate KGF-2, another growth factor that can also be used for wound treatment. KGF-2 is very closely related to KGF, yet only KGF-2 is inactivated by plasmin or plasminogen. This fact clearly underscores the subtle difference between these two growth factors and the non-obviousness of the particular claimed combination between KGF and plasmin or plasminogen. A combination of plasmin or plasminogen and other growth factors would likely lead to the inactivation of the growth factors. However, the combination of KGF and plasmin or plasminogen by the Applicants produced unexpected results by behaving synergistically in the treatment of wounds. See Specification, page 19, lines 13 – 27.

An applicant may rebut a *prima facie* case of obviousness by showing that the prior art teaches away from the claimed invention in any material respect. See *In re Geisler*, 116 F.3d 1465, 1469, 43 USPQ2d 1297, 1365 (Fed. Cir. 1997). Furthermore, the totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. See *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).

For anyone of ordinary skill in the art, the consideration to combine two or more agents is driven by the desire for the enhanced effect and the feasibility to combine them. For example, it would not be advisable to combine an acidic drug with a basic drug as the combination would lead to neutralization or complex formation, thus eliminating the effect of both drugs. In the current application, a protein and a protease enzyme are combined.

A protease enzyme, or protease, is defined as: “an enzymatic protein that breaks down other proteins.” See Drlica, Karl, Understanding DNA and Gene Cloning, 2004, p. 351 (Exhibit 1).

Applicants assert that the combination of a first element with a second element, when the second element is commonly known to digest and destroy the first element, is not an obvious combination. It is well taught to everyone of skill in the art that a protease is an enzyme that digests or destroys a protein. Thus, it is apparent that a protein and a protease should not be combined, because the protease can digest or inactivate the protein. Not only is there a complete absence of motivation to make such a combination, but the common knowledge in the art actually teaches away from the combination of a protein and a protease enzyme. Furthermore, Applicants proceeded contrary to the accepted wisdom in the art to achieve such a combination, so the combination is not obvious.

Before obviousness may be established, the Examiner must show that there is either a suggestion in the art to produce the claimed invention or a compelling motivation based on sound scientific principles. Logic compels that the suggestion or motivation be accompanied by a general knowledge of the existence of art-recognized techniques for carrying out the proposed invention. See *Ex parte Krantz*, 19 U.S.P.Q.2d 1216, 1218 (B.P.A.I. 1990). Furthermore, the

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motivation to make a specific invention is not abstract, but practical, and is always related to the properties or uses one skilled in the art would expect the invention to have, if made. The critical inquiry is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. *See In re Newell*, 891 F.2d 899, 13 U.S.P.Q.2d 1248, 1250 (Fed. Cir. 1989).

The prior art contains absolutely no suggestion or motivation that would compel a person of skill in the art to combine a protein and its inherently antagonistic protease enzyme. Such a combination is completely contrary to sound scientific principles. The Examiner has pointed to nothing in the prior art which would suggest the desirability of making such a combination. Thus, lacking motivation to do so, it would not have been obvious to one of skill in the art to combine a protein with its classic antagonist, a protease enzyme.

II. Conclusion

In summary, the claimed combination of a protein and a protease enzyme is not obvious because (1) there was no reasonable expectation of success, (2) the prior art teaches away from combining two antagonistic components, (3) Applicants proceeded contrary to the accepted wisdom in the art to arrive at the claimed combination, and (4) there was a complete lack of motivation in the prior art to make such a combination.

For the reasons stated above, Applicants respectfully submit that Claims 1, 3, 5, 7, 13 – 15, 17, and 23 – 25 are patentable.

If the Examiner has any other matters which pertain to this Application, the Examiner is encouraged to contact the undersigned to resolve these matters by Examiner's Amendment where possible.

Respectfully submitted,



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